PHASE RESPONSE OF MODEL SINOATRIAL NODE CELLS - AN INVESTIGATION OF THE INFLUENCE OF STIMULUS PARAMETERS

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Abstract- **When a brief current pulse is incident on cells in cardiac and other nervous tissue, a change in phase of the cell's response is usually observed. In cardiac tissue, the cells are exposed to external stimulation of mainly positive currents, which depolarise the cells (except for some ACh interactions).**
There are a number of factors that influence the phase response of the cell. These include the timing of the stimulus, its magnitude, duration and polarity. The interbeat interval of the cell may be prolonged or shortened, causing a steady state phase offset from the original cycle. The particular phase response is dependent on the stimulus parameters.
We investigate the phase response of a model sinoatrial node cell when subjected to single depolarising stimuli as a function of the stimulus parameters. The model used was developed by Dokos [1] which defines the ionic currents that cause the spontaneous electrical activity of the cells.
Keywords **- Phase response, sinoatrial node**

I. The Phase Response Curve

The application of brief pulses of current to sino-atrial pacemaker cells may result in phase-dependent changes in the cell's cycle length. When applied in a periodic fashion, this can force the pacemaker to beat at a cycle length different from its intrinsic cycle length. In general, these applied pulses do not affect the amplitude or the shape of the pacemaker cell action potential. The magnitude and direction of the phase shift depend on the timing as well as on the intensity and duration of the stimulus.

The effects of the external stimuli over the cell's cycle of activity can be summarised as a Phase Response Curve (PRC). This curve defines the phase shift of the discharge of the pacemaker cell with constant intrinsic cycle length as a function of phase at which an external stimulus is applied to the pacemaker action potential. In this study, the maximum downstroke gradient of the pacemaker action potential is taken to be the reference point, i.e. the point of zero phase. The phase ϕ is then defined as $\phi = t/\tau$, when t is the time of stimulus onset and τ is the period of the unperturbed cell cycle. The phase shift, $\Delta\phi$, is either an advance or a delay of the phase, lengthening or contracting the cell's cycle after the stimulus. In general, a pulse applied early in the cycle prolongs that cycle, as opposed to later in the cycle, whereupon it shortens it (see for instance [2], [3]). An approximation of the cardiac PRC is a linear function of $\Delta\phi$ with ϕ. The slope can be related to fundamental parameters of the oscillator.

Physiological data shows phase shifts in aggregates of ventricular cells [2], both embryonic and adult [4], as well as single sinus cells [5]. Simple Hodgkin-Huxley type ionic models model this effect quite well. More complex models, however, also fit the PRC as well as matching other physiological measurements.

Here we use a complex ionic model to show the effect on the PRC of different stimulus parameters. A computer model of a pacemaker cell is built around the ionic current model of Dokos [1]. Simulations were then made of this cell subjected to external stimulation.

This model allows us to investigate the phase response of the pacemaker cell resulting from different magnitude and different duration current stimuli.

Physiological recordings of cells and their response to external stimuli usually take the form of responses to pulse trains. It has also been observed experimentally that the period of the cell's cycle does not significantly change in those cycles post the stimulation period [5]. This leads to the hypothesis that there is no "memory" effect in the cell; that is, the spontaneous cycle length is unchanged after applying a single pulse to the system. We have found in simulation experiments on our model cell that this is indeed the case (see [6]).

When a stimulus is singly applied to the cell, only the cycle in which it is applied is affected. The cell's cycle appears to revert to its intrinsic length, frequency and shape in cycles after a single pulse.

II. Ionic Currents contributing to membrane potential

The Dokos model [1] is a Hodgkin-Huxley [7] based cell model with nine membrane currents representing individual ionic contributions. We refer the reader both to our paper [6] and to the paper by Dokos [1] for a complete description of the model.

III. Simulations

The cell was modelled using GENESIS, the Generic Neural Simulation System [8]; implementing each of the currents of the Dokos model as well as the relevant concentrations. A single cylindrical cell was simulated, 100μm in length, 8μm in diameter, yielding a surface area of $2613(\mu m)^2$. The capacitance of the cell was taken to be 32pF. Stable initial values were derived from reference [1]. A fuller description of the modelling process can be found in reference [6]. The period of the model cell's cycle was found to be approximately 0.384s.

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Abstract

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IV. Simulation Results

Depolarising pulses of varying magnitudes and durations were applied to the model system at times to systematically scan the unperturbed cell's cycle. In this way phase response curves (PRC) were constructed for each pulse type.

The phase of the perturbed cycle was measured by ascertaining the times at which the maximum downstroke of its cycles occurred. This zero phase point was chosen to minimise problems associated with false points due to the depolarising pulse transients. Additionally, we required that the zero phase points occurred at approximately the same membrane potential. The time between the first unperturbed zero phase point and the time of the stimulus was then determined. The phase of the onset of the stimulus, ϕ, is this time divided by the period of the unperturbed cycle.

Subsequent zero phase points and the phase of these points relative to the unperturbed cycle were then calculated. Due to the fact that there is no memory effect in this system [6], all subsequent cycles were shifted by the same phase relative to the unperturbed cycle.

Simulations were performed using pulse durations from 0.25ms to 100ms, with pulse magnitudes ranging from 0.1nA to 5nA. The onset phases for the simulation experiments ranged over the whole cell cycle. In a series of simulations, the phase resetting of the model cell was investigated as a function of pulse magnitude, pulse duration as well as the onset phase of the stimulus.

An example of the PRC obtained for the model cell is shown in Fig. 1. This PRC is for stimuli of 0.5, 1 and 2nA, all of duration 1ms. Note that as the stimulus magnitude increases the PRC takes on a "sawtooth" shape, corresponding to near complete entrainment of the model cell to the stimulus. Some parts of the PRC, specifically around 0.8-0.9 are relatively fixed and only have small phase responses for the whole range of stimuli. This region is around the maximum upstroke gradient to the peak of the beat, and although the cell may deviate from its limit cycle when perturbed at these points (see [6]), the phase response is very small – the cell is already entrained. The "sawtooth" curve represents the maximum limit of phase response for the cell under stimulation.

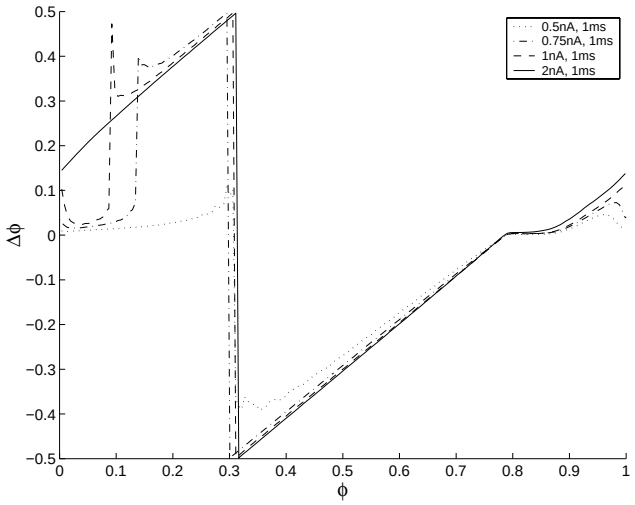

Fig. 1: PRC for stimuli of 0.5, 0.75, 1 and 2nA, duration 1ms. Note that as the stimulus magnitude increases, the PRC takes on the "sawtooth" shape, characteristic of complete entrainment of the cell. The region of ~0.8-0.9 is the upstroke and maximum of the beat, and shows little phase movement, as the beat is already occurring at this point.

If we look at the phase response of the model cell as a function of stimulus magnitude, fixing both the stimulus duration and onset phase, we obtain trends such as shown for the examples in Fig. 2.

Fixing the onset phase and stimulus magnitude, we also obtain the phase response as a function of stimulus duration. Examples of this are shown in Fig. 3.

Note that in both Fig. 2 and 3 that the phase response has

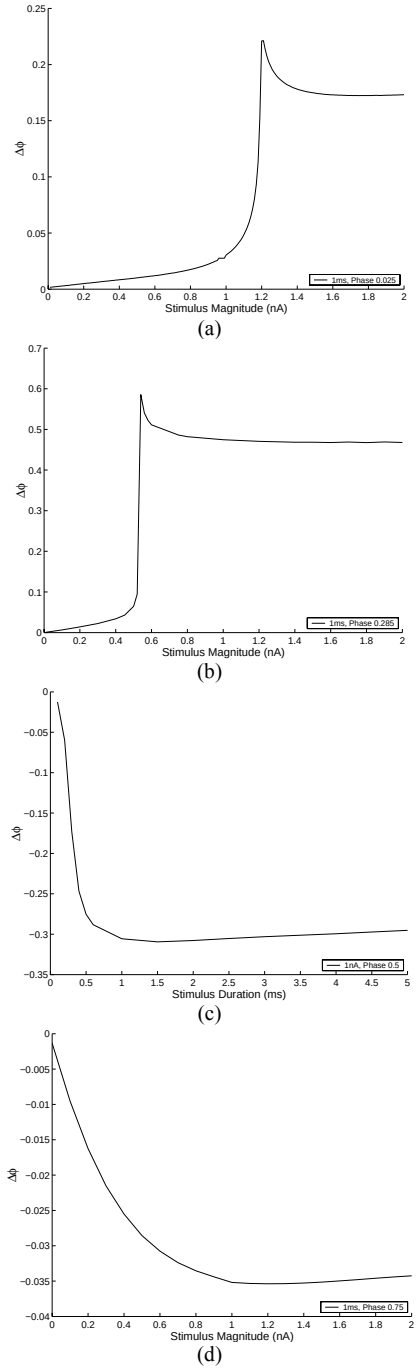

Fig. 2: Phase response as a function of stimulus magnitude, for stimuli of duration 1ms, for onset phases of (a) 0.02, (b) 0.285, (c) 0.5 and (d) 0.75. Note the transitions of the curves to steady values as the magnitude increases.

a transition to a steady value with increasing stimuli. After this transition the phase response plateaus.

This plateau value of the phase response corresponds to the complete entrainment of the model cell, and is itself a function of the onset phase (c.f. the "sawtooth" PRC of Fig. 1).

Similar trends were observed for the entire range of stimulus parameters investigated.

Using the simulation data, it is possible to define the stimulus characteristics required to cause a particular phase response. Fig. 4 shows the pulse characteristics required to produce a phase shift of magnitude 0.2, for fixed onset phases, with stimulus duration plotted versus stimulus magnitude.

Note that, irrespective of the onset phase, the trends in Fig. 4 are hyperbolic. This broadly indicates that, in order to achieve the phase shift, the stimulus has to be either short and large in magnitude, or longer in duration and smaller.

This was also the case for other phase shifts and onset phases. This concurs with commonly accepted physiological findings in other excitable tissues.

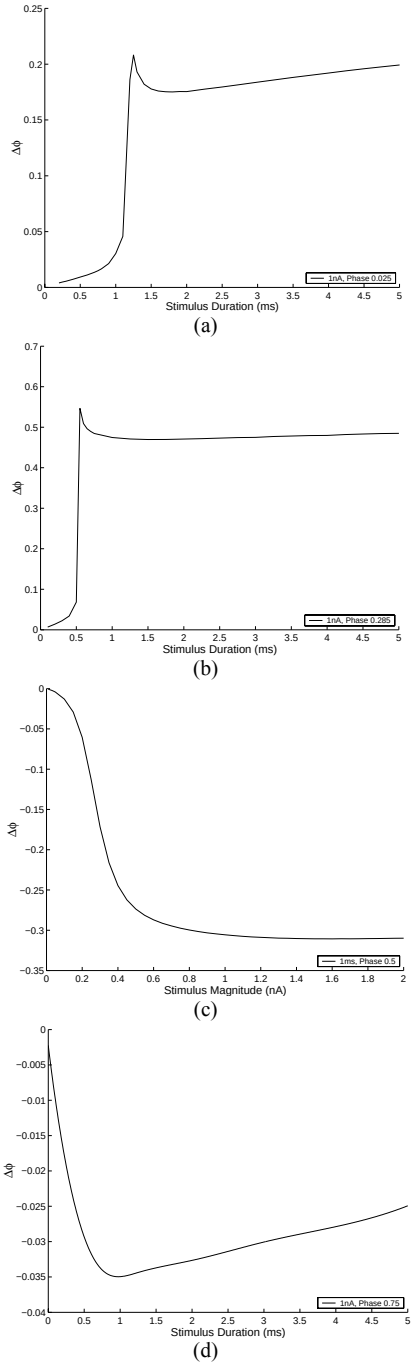

Fig. 3: Phase response as a function of stimulus duration, for stimuli of magnitude 1nA, for onset phases of (a) 0.02, (b) 0.285, (c) 0.5 and (d) 0.75. Note the transitions of the curves to steady values as the magnitude increases.

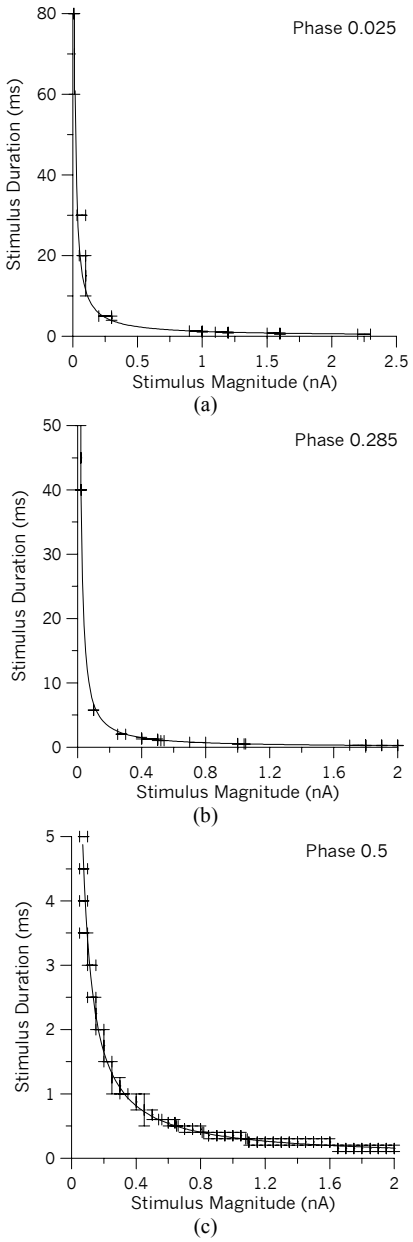

Fig. 4: Stimulus Characteristics required to cause a phase shift of 0.2 magnitude, for onset phases of (a) 0.02, (b) 0.285 and (c) 0.5.
The error bars indicate the uncertainty due to the discrete sampling and identifying the transition through ±0.2.
Note that no stimulus when onset at 0.75, no matter how long in duration nor large in magnitude, caused a phase response greater than 0.2 in magnitude. As can be seen in both Fig. 1 and 2, the maximal phase response at this onset phase is only about –0.035.

Given the stimuli required for a particular phase response at a particular onset phase, we can calculate the charge transferred during the stimuli. Fig.5 shows the charge transferred for an onset phase 0.5, to cause a phase response of -0.2. Note that the charge transferred during the stimulus remains approximately constant, regardless of the particular makeup of the stimulus parameters. This was also found to be the case for all the different scenarios of required phase response and onset phases.

V. Discussion

The phase response of our model cardiac cell shows characteristics resembling experimentally observed phase responses in the sinoatrial node [6].

We have observed that there are transitions in the phase response as a function of stimulus magnitude and as a function of stimulus duration (see Fig. 2 and 3). Generally, the phase response of the model cell is very small up until a transitional value whereupon it "jumps" to the entrained value for that onset. (This transition is particularly sharp for earlier onsets). Thus to obtain significant (or the entrained) phase responses, the stimuli characteristic can be extracted from the transition points of the plots such as Fig.2 and 3.

We have also been able to show that there is a clear relationship between the magnitude of the phase response and stimulus characteristics, specifically the hyperbolic relationship of stimulus duration and magnitude (for example Fig. 4) for a given phase response.

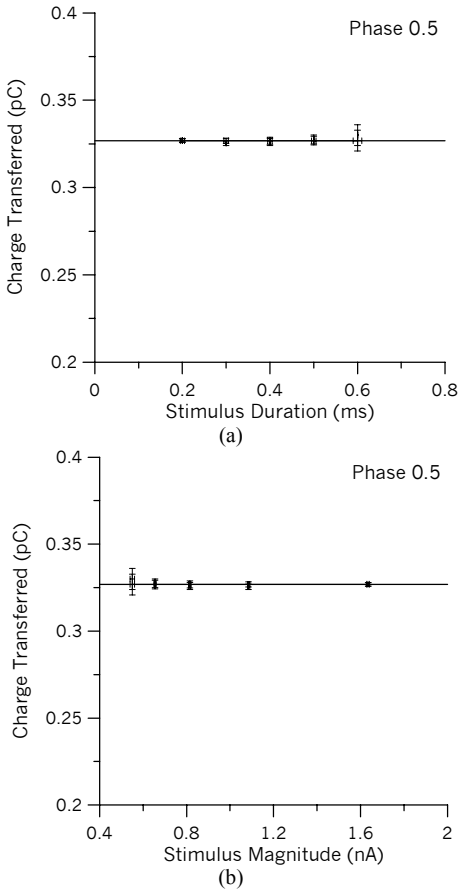

Fig. 5. Charge Transferred for stimuli causing a -0.2 phase response versus (a) the stimulus duration and (b) versus the stimulus magnitude, for onset phase 0.5. The error bars indicate the uncertainty due to the discrete sampling and identifying the transition through –0.2 phase response.

In this case, the stimuli were also found to have the same charge (Fig. 5). So, it is not the particular characteristics of the stimulus but the total charge transferred to the cell that causes the phase response. This holds for stimuli up to about 20ms in duration. Longer stimuli have some more profound effects, and this is to be the subject of a further investigation.

VI. Conclusion

The investigation of the influence of stimulus parameters on the phase response of our model cell, specifically the hyperbolic relationship between stimulus magnitude and duration for fixed phase responses has encouraging parallels with commonly accepted ideas about the stimulus response curves of nearly all excitable tissue. This is both unexpected and encouraging.

Additionally, the fact that the stimulus characteristics required for a specific phase response of the cell may be extracted from our study may have implications in the future design and optimisation (both for effect and energy consumption) of neurostimulators. This is especially interesting given that some artificial pacemaker systems now have the ability to detect the phase of the cells requiring phase shifts.

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